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Predictive value of EEG in postanoxic encephalopathy: a quantitative model-based approach.

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Abbreviations:

ACNS: American Clinical Neurophysiology Society

AED: antiepileptic drugs

ANS: autonomic nervous system

cmri: cerebral magnetic resonance imaging

cCT: computer tomography

CPC: Glasgow-Pittsburgh cerebral performance categories

CPR: cardiac resuscitation procedure

ED : epileptic discharges

EEG: electroencephalogram

FFT: fast Fourier transformation

HRV: Heart-rate variability

ICU: intensive care unit

PPV: Pulse pressure variability

ROC: Receiver operating characteristic (ROC)

SEP: somatosensory evoked potential

TWs: triphasic waves

ABSTRACT

Introduction:

The majority of comatose patients after cardiac arrest do not regain consciousness due to severe postanoxic encephalopathy. Early and accurate outcome prediction is therefore essential in determining further therapeutic interventions. The electroencephalogram provides a standardized and commonly available tool for measuring brain activity and has been used to determine prognosis in postanoxic patients. The identification of pathological EEG patterns with poor prognosis relies however primarily on visual EEG scoring by experts. We introduced a model-based approach of EEG analysis (state space model) that allows for an objective and quantitative description of spectral EEG variability.

Methods:

We retrospectively analyzed standard EEG recordings in 83 comatose patients after cardiac arrest between 2005 and 2013 in the intensive care unit of the University Hospital Zürich. Neurological outcome was assessed one month after cardiac arrest using the Cerebral Performance Category. For a dynamic and quantitative EEG analysis, we implemented a model-based approach (state space analysis) to quantify EEG background variability independent from visual scoring of EEG epochs. Spectral variability was compared between groups and correlated with clinical outcome parameters and visual EEG patterns.

Results:

Quantitative assessment of spectral EEG variability (state space velocity) revealed significant differences between patients with poor and good outcome after cardiac arrest: Lower mean velocity in temporal electrodes (T4 and T5) was significantly associated with poor prognostic outcome ($p<0.005$) and correlated with independently identified visual EEG patterns such as generalized periodic discharges ($p<0.02$). Receiver operating characteristic (ROC) analysis confirmed the predictive value of lower state space velocity for poor clinical outcome after cardiac arrest (AUC 80.8, 70% sensitivity, 15% false positive rate).

Conclusion:

Model-based quantitative EEG analysis (state space analysis) provides a novel, complementary marker for prognosis in postanoxic encephalopathy.

INTRODUCTION

The majority of comatose patients after cardiac arrest do not regain consciousness due to severe postanoxic encephalopathy [1–4]. In absence of rapid recovery of consciousness after cardiac arrest, early and accurate outcome prediction is therefore essential for determining further therapeutic interventions according to the patients' best interest. In particular, reliable measures for poor prognosis may provide guidance in identifying those patients in whom withdrawal of support must be considered. The electroencephalogram (EEG) provides a standardized and commonly available tool for measuring brain activity and has been used to determine prognosis in postanoxic patients [5–8]. Various electroencephalographic patterns, including iso-electric EEG, low-voltage pattern, burst suppression or generalized periodic discharges, independently correlate with poor clinical outcome [9], with higher specificity in multimodal diagnostic approaches including assessment of SSEP and MRI [8,10,11]. The identification of pathological EEG patterns with poor prognosis relies primarily on visual scoring by EEG experts, whereas recent approaches also include quantitative EEG measures, e.g. inter-hemispheric synchronization, transfer entropy or cross-correlation of burst-shapes [12–14]. Similarly, quantitative EEG analysis, based on probabilistic description of spectral temporal symmetry, can detect EEG reactivity in coma [15]. Patients with potential for good recovery might be more difficult to identify based on EEG, but fluctuating background activity and EEG reactivity to external stimulation are predictive factors for favorable outcome [16].

Although the underlying mechanisms generating postanoxic EEG patterns might be different in each case, a consistently present element in patients with poor outcome is the low temporal variability of the EEG. For example, status epilepticus, generalized periodic discharges or burst suppression are unequivocally characterized by monomorphic EEG discharges without significant temporal evolution. In the case of burst suppression, identical burst morphology does correlate itself with poorer outcome after hypoxia: i.e. monomorphic EEG pattern correspond to poor clinical outcome [12,17]. In this line, the temporal variability of the EEG background might serve a prognostic factor in the evaluation of postanoxic EEG. However, subtle temporal fluctuations of background activity are particularly difficult to assess by visual scoring of

EEG epochs in a fixed time frame and might be better approachable by quantitative EEG analysis.

We recently introduced a model based approach of EEG analysis (state space model) that allows for a quantitative description of temporal EEG variability. This model has previously been established in sleep EEG analysis. This apporach describes EEG data in a 2-dimensional state space and translates the temporal spectral variability into trajectories within a mathematical space [18–21]. In the context of postanoxic coma, we hypothesize that this approach allows for an unbiased and quantitative assessment of spectral variability in the surface EEG signal, hereby providing further clinically relevant information regarding recovery from postanoxic encephalopathy.

We performed a retrospective cohort study to examine whether spectral EEG variability as measured in the state space model may serve as an additional, objective and quantifiable predictor for outcome after cardiac arrest.

METHODS

Subjects and study protocol

We included 83 comatose patients (age: 60±15 years, 57 male, 26 female) resuscitated following cardiac arrest between 2005 and 2013 in the intensive care unit (ICU) of our clinic. All patients with documented cardiac arrest and EEG examination after resuscitation were screened for study inclusion. Exclusion criteria were known neurodegenerative disease before cardiac arrest, severe traumatic brain injury, or patients who prospectively declined the use of their data for study purposes. Patients were treated by standardized protocols based on clinical decisions; mild therapeutic hypothermia was applied in 35 patients. In all patients treated with hypothermia, EEG assessment was performed after rewarming. Neurological outcome was assessed one month after cardiac arrest based on review of clinical records and rehabilitation reports (including therapy assessments) and graded according to Cerebral Performance Category [22]. Survivors with CPC 1 or 2 were classified as "good" and patients with CPC 3-5 as "poor" outcome. Patient demographics and clinical parameters are shown in Table 1. Details regarding data collection and outcome analysis was peformed as described previously [23] . The study protocol was approved by the local ethical board (*Kantonale Ethikkommision of the Canton Zurich*).

EEG recordings

We acquired standard EEG recordings off sedation with needle or pad electrodes according to the International 10-20 system for electrode placement with additional subtemporal electordes (T1/T2) and bipolar one-channel electrocardiogram (Nihon Kohnden EEG-1100 recorder). The minimal required EEG duration was 20 minutes. Response to external stimuli was assessed in all patients following a standardized protocol (bilateral acoustic and painful stimuli) and correlated with clinical (movement, eye opening) or electroencephalographic responses (time-locked changes of EEG background). Visual EEG analysis was performed on blinded data by two experienced specialists (R.P. and R.R.). EEG patterns were classified according to standardized ACNS criteria [24] classifying background activity, reactivity to external stimuli, and occurrence of generalized discharges (GPDs). Burst suppression pattern were classified

as described earlier [23]. In patients with several EEG recordings at different time points (20 cases), the first EEG after cardiac arrest was used for the correlative outcome analysis.

State Space Model

To allow for a dynamic and quantitative analysis of postanoxic EEG, we implemented a model-based approach (state space analysis). This method has previously been established and validated for EEG analysis in healthy and pathological sleep in rodents and humans [18–20]. A mathematical description and a review of previous applications can be found in [25]. Briefly, in state space analysis, the spectral information of each 5s EEG-epoch is transformed to a 2-dimensional state space by means of previously defined frequency bands of the corresponding frequency spectrum. By calculating two different frequency ratios, each 5s EEG epoch is represented as a point in a 2-dimensional state space: 20 minutes of EEG recording can therefore be described as a scatterplot containing 240 points (Figure 1, black points).

We implemented the model based EEG analysis as follows: The raw data traces were re-referenced to a common average montage (linked ears) and each channel was subdivided into 5s-epochs. Then, a fast Fourier transformation (FFT) was applied on each 5s-epoch after multiplication by a Hann window. Next, we determined the frequency ratios as derived from the fixed frequency bands for each epoch (parameters: Ratio1 = (8.6–19.3 Hz)/(1.0–10.9 Hz), Ratio2 = (11.5–20.3 Hz)/(17.9–31.5 Hz)). Finally, we calculated velocities in state space as the distance between two subsequent states divided by the time interval between these states [20].

In previous studies focusing on sleep EEG, we showed that phases of consolidated EEG states correspond to low variability in state space, (e.g. consolidated NREM sleep, Figure 1), whereas transitional sleep states are represented by trajectories in state space. In other words, changing position in state space translates to variability of the underlying EEG trace. Transitional EEG states can therefore be characterized by higher velocity in state space. Accordingly, previous studies showed that velocity in state space corresponds to EEG variability and can be used to quantify the temporal fluctuating pattern of sleep EEG in healthy and pathological sleep [20]. For example, in a study in Parkinson's patients we found earlier that lower state space velocity represented

impaired sleep-wake dynamics [21]. In summary, the model based-approach provides objective and quantitative measures with special emphasis on EEG variability. In the setting of coma EEG, we therefore used this model to quantify background variability independent from visual scoring of subsequent epochs.

Statistical Analysis

We used χ^2-tests for comparison of categorical variables and student t-tests for continuous measures between groups. State space velocity for each channel was compared between groups using nonparametric permutation test, accounting for multiple comparisons [26]. Clinical outcome and mean velocity measures were correlated with clinical parameters and visual EEG pattern by multivariate logistic linear model analysis. Receiver operation characteristic analysis was performed to test the performance of state space velocity as a binary classifier.

RESULTS

Study population

We identified 119 patients after cardiac arrest from a previously established clinical EEG database [23] who fulfilled all inclusion criteria. We excluded 25 patients with severe EEG artifacts, short EEG duration (<20min) or patients in whom no standardized reactivity testing was performed during the EEG. The final sample size was 83 patients (24 female, age 60.1±15.8 years). We identified the most likely cause of cardiac arrest in all patients by review of the patients' history and identified 32 patients with myocardial infarction, while 15 suffered from non-ischemic heart disease. Other frequent reasons leading to cardiac arrest were asphyxia (7), traumatic injury (5), and hypovolemic shock (5). Overall, 19 patients (23%) survived with no or moderate deficits (CPC 1-2), 64 patients (77%) were classified as poor outcome (CPC 3-5). EEG recordings were performed upon clinical indication, on average 3.5±2 days after cardiac arrest. Pairwise comparison revealed a better outcome in younger patients and patients with non-ischemic cardiac disease (Table 1).

Analysis of state space clusters:

State space analysis of raw EEG recordings showed well-defined and separable clusters of coma EEG in all individuals. Comparison with state space clusters from previous sleep studies [20], revealed that the coma cluster was clearly separated from other sleep states including waking state (illustrated for one individual in Figure 1). In other words, the model assigned coma neither to wakefulness nor sleep, but as a distinct separable behavioral state.

To identify quantitative predictive measures in post-hypoxic coma, we first compared location, temporal dynamics and spatial variability of state space clusters between patients with good and poor outcome. Patients with good outcome showed a higher variability of EEG trajectories in state space, reflected by the larger distribution of clustered points and broader probability density distribution in state space (Figure 2A). Conversely, in patients with poor outcome, EEG clusters showed lower variability (Figure 2B). To quantify these observations, we included cluster location, spatial

variability (standard deviation in both dimensions) and velocity in state space (i.e. temporal variability) in a multidimensional logistic general linear model to predict outcome (good vs poor). Higher velocity in state space was significantly correlated with good outcome, whereas cluster location and spatial variability was unchanged between both groups (Table 2).

Higher velocity in state space correlates with good outcome

We then compared the identified predictive factor (state space velocity) between patients with poor and good outcome for all electrode locations. We found significant differences predominantly in temporal and less in frontal electrodes (Fp1 F8, T3, T4, T5, T1, T2, O1, Figure 3). We observed the highest difference in mid-temporal electrodes (T4: $p< 0.001$ and T5: $p<0.016$ after correction for multiple comparisons). Comparison of mean velocity (all electrodes) for both groups revealed also significant difference between patients with poor and good outcome (good: mean: 0.83±0.17 poor: 0.73±0.17; $p< 0.01$).

Estimated power of temporal state space velocity as a predictive outcome measure

We included temporal velocity in state space in a multilinear logistic model to predict outcome (good vs. poor) controlling for possible clinical confounding factors (e.g. age, anticonvulsive treatment or hypothermia). This analysis confirmed the significant correlation of higher temporal velocity with good outcome (Table 3). Similarly, in a bivariate regression analysis we found a linear relation between outcome (quantified by CPC) and state space velocity (Figure 4). To assess the diagnostic value of temporal state space velocity, we finally performed a receiver operating characteristic (ROC) analysis. This analysis confirmed the predictive value of lower state space velocity for poor clinical outcome after cardiac arrest (AUC: 80.8%). Depending on the applied cut-of value, state space velocity can be used as a marker with high sensitivity (70%), but 15% false positive rate (limit 0.75) or lower sensitivity, but 100% specificity (limit 0.5, Figure 4B).

Finally, we tested for an association of state space velocity with known visual EEG parameters for poor outcome in hypoxic encephalopathy, such as backroundreactivity,

backroundvariability, epileptic discharges, generalized periodic discharges, or burstsupresssion pattern. We found associations of state space velocity with burst suppression pattern and generalized periodic discharges, but other EEG markers did not correlate with state space velocity (Table 4). The time point of EEG examination after cardiac arrest was included as a co-variate in all models, but did not influence temporal state space velocity or the predictive value. The odds ratio in patients with burst suppression was significantly larger than 1, implying that burst suppression was associated with higher state space velocity.

DISCUSSION

In this retrospective cohort study, we implemented a novel quantitative model-based approach to predict clinical outcome from EEG recordings independent from subjective EEG interpretation. The core finding of our study was that higher spectral variability in a standard EEG (as measured by velocity in a state space model) correlated significantly with good outcome after cardiac arrest. This finding provides proof of principle that the implemented model-based approach is useful for predicting outcome in post-hypoxic coma independently from other visual EEG analysis.

EEG is commonly used to evaluate prognosis in comatose patients after cardiac arrest and various EEG patterns are known to be associated with poor prognosis. However, varying definitions of 'malignant' EEG patterns, influence of sedation, or inter-rater variability of visual EEG interpretation, are important limiting factors for using EEG in prognostication after coma. Furthermore, whereas distinct patterns such as periodic discharges or burst suppression are classified with high inter-rater agreement [27] other EEG markers such as background reactivity or background continuity show only moderate inter-rater agreement, applying the current ACNS criteria [15]. Further bias arises from the fact that in a clinical setting, EEG assessment is usually performed in an un-blinded manner. Identification of a pattern with suspected poor outcome might therefore support the decision for withdrawal of care, hereby directly influencing its prognostic value ("self-fulfilling prophecy") [28]. A model-based approach on the other hand allows for a rater-independent, objective and quantitative assessment of coma EEG. However, does the identified prognostic marker (state space velocity) truly add novel information about the underlying EEG (and the coma patient) beyond already known patterns associated with poor outcome? In the performed multivariate analysis state space velocity did not correlate with visual assessment of EEG background variability, background reactivity or EEG voltage and we found even an inverse relation to burst suppression. Whereas this might rise concern for the significance of its predicting value of per se, in contrary, we argue that lack of association with visual EEG patterns underlines the objectivity of our method. In particular, EEG background variability is difficult to assess by visual scoring and has therefore only limited relevance

as a prognostic factor as of yet. The automated assessment of spectral variability by means of the state space model, however, shows a strong association with coma outcome. We therefore conclude that the concept of using EEG background variability as a prognostic factor in comatose patients is valid, but can only properly be quantified and eventually correlated with outcome in a model-based approach independent from human scoring. The positive correlation of state space velocity with burst-suppression indicates that patients with burst-suppression have higher state space velocity. This finding might be an effect of rapidly changing spectral properties of the EEG in the state of burst suppression (burst vs. low voltage EEG), which translates to a higher velocity in the model. This implicates that in occurrence of burst suppression state space velocity might falsely indicate a good outcome and must be interpreted with caution (or not be assessed at all). On the other hand, it should be considered that the prognostic value of the model would show a higher sensitivity, if patients with burst suppression pattern were excluded from the analysis.

This study has several limitations. Primarily, the retrospective inclusion of patients provides potential biases on different levels. In particular, the quantification of the prognostic value must be interpreted with caution and was performed only to test the usefulness of state space velocity as a potential quantitative biomarker on a proof-of-principle level. Our data does not provide sufficient evidence to use state space velocity in the clinical evaluation of coma patients and ultimately its prognostic value should be assessed in a prospective approach in future studies. Furthermore, many confounding parameters such as time of EEG recording, use of anticonvulsive drugs or hypothermia vary between subjects and were changed based on clinical grounds. Although we controlled for these factors in the multivariate analyses, a systematic influence on the reported quantitative measures cannot be ruled out. Nevertheless, we performed the model based data analysis and assessment of outcome in a double blinded manner (analysis of patient history: RR and EE; data modeling: LI) without modifying the previously established model. Therefore, we argue that the observed associations reflect a significant relation between clinical outcome and the model based analysis.

Coma is considered to be a global (dysfunctional) brain state and visual inspection of EEG in comatose patients usually shows little local variability. Nevertheless, we observed higher state space velocity in patients with good outcome predominantly in temporal electrodes. The reason for this temporal predominance remains elusive. One might argue, that higher EEG variability in temporal regions is linked to more activity in temporal limbic structures representing regulatory function of the autonomic nervous system. Heat rate variability which is also linked to temporal (dys-) function e.g. has been shown to be a predictive parameter in coma patients after TBI [29] and a similar mechanism might be at play in postanoxic coma. Alternatively, the temporal predominance of spectral variability might be linked to re-emerging physiological activity of cortico-subcortical resting state networks such as parieto-temporal resting oscillatory activity [30]. Our findings could then suggest that the higher variability in the temporal lobe represents an early sign for regaining normal resting network function after cardiac arrest.

In conclusion, state space velocity provides a novel quantitative measure correlating with outcome in coma after cardiac arrest independently from visual EEG pattern with poor prognostic value. The independence from human expert scoring and the quantifiable approach are advantages over current state-of-the art visual interpretation of EEG traces, but future prospective studies will have to verify its prognostic value alone or in combination with other quantitative and qualitative predictive biomarkers.

Table 1: Patients Demographics

	Total (83)	Good (19)	Poor (64)	p-value
Age [y]	60 (15)	53 (19)	62 (13)	**0.01**
Gender	f/m: 26/57	7/12	19/45	0.38
Down time (ROSC) [min]	21.3 (15.1)	18.6 (22.9)	21.0 (10.9)	0.85
Hypothermia (y/n)	35/83	8	27	0.99
Timepoint of EEG [d]	3.5 (2.7)	4.2 (3)	3.2 (2.5)	0.27
Cause of cardiac arrest				
Myocardial ischemia	32	6/19	26/64	0.47
Non-ischemic cardiac disease	15	7/19	8/64	**0.01**
Non cardiac causes	36	5/19	31/64	-

Table 1: Patient demographics of all included patients (Total) and subgroups with good and poor outcome. Mean values (SD) and proportions are shown for each group. f: female, m: male. Down time: calculated as the length of time between the patient being recognized as pulseless and ROSC (documented in 44 cases). Timepoint of EEG: time of EEG recording after cardiac arrest. Cause of cardiac arrest: 'Non cardiac causes' include asphyxia (n=7), traumatic injury (n=5), and hypovolemic shock (n=5). aortic dissection (n=1), pulmonary embolism (n=1), intoxication (n=1), hypovolemic shock (n=2), and unclear (14 cases). P-values are calculated using 2-sided t-tests or $\chi 2$-tests as appropriate.

Table 2 : Multilinear logistic model predicting good outcome after cardiac arrest from state space variables

Variable	β-coefficient	Std. Error	z-value	p-value
Velocity	6.36	2.52	2.52	**0.01**
Meanx	-0.16	0.33	-0.49	0.63
Meany	-0.43	0.51	-0.85	0.40
Var(x)	-1.17	0.90	-1.30	0.19
Var(y)	1.73	1.61	1.07	0.28

Table 2: Unstandardized correlation coefficients (β-coefficient) for state space parameters versus clinical outcome; positive values predict better outcome. Velocity: Average state space velocity, Meanx: mean cluster location in the x-axis in the scatterplot, Meany: mean cluster location in y axis in the scatterplot. Var(x/y): Variability of clusters in both dimensions.

Table 3: Multilinear logistic model predicting good outcome after cardiac arrest from state space velocity controlled for clinical parameters.

Variable	β-coefficient	Std. Error	z value	p-value
Velocity	7.46	3.29	2.27	**0.02**
Timepoint of EEG	-0.13	0.19	-0.66	0.51
Gender	-0.18	1.04	-0.18	0.86
Age	-0.07	0.04	-1.54	0.12
AED	0.39	1.25	0.31	0.76
Down time (ROSC) [min]	-0.02	0.04	-0.43	0.67
Hypothermia (n/y)	1.45	1.08	1.34	0.18

Table 3: Multilinear logistic model for outcome prediction based on state space velocity in state space controlled for possible clinical confounding factors: Time point of EEG, Age, AED: anticonvulsive treatment, Down Time (defined as in Table 1), Hypothermia. β-coefficient: unstandardized correlation coefficient.

Table 4: Odds ratios of correlation between state space velocity and EEG patterns.

Variable	OR	2.50%	97.50%	p-value
GPD	0.91	0.83	1.00	**0.05**
Backgroundreactivity	1.05	0.94	1.18	0.37
ED	1.18	0.89	1.56	0.26
Backgroundvariability	0.97	0.89	1.07	0.57
Backgroundvoltage	0.98	0.93	1.03	0.41
TWS	1.12	0.93	1.36	0.25
Burst Suppression	1.39	1.19	1.62	**<0.005**

Table 4: Odd's Ratios (OR) derived from multilinear regression model correlating state space velocity with visual EEG patterns (GDP: generalized periodic discharges, ED: epileptic discharges, TWS: blunt triphasic waves). Velocity correlates negatively with GPD and positively with burst suppression EEG. Limits of the 95% confidence intervals are given for each OR (columns: 2.5% and 97.5%).

Figure Legends:

Figure 1: State space representation of coma EEG mapped in a 2-dimensional state space in a single subject. Each 5 s epoch is represented by 2 different EEG frequency ratios plotted on log/log axes. 20 minutes coma EEG recording is represented by clustered black points in the left lower corner. For comparison, sleep EEG clusters are shown for a control subject (data from: [21]). Color coding of the clusters is based on model-based sleep scoring for WAKE (red), NREM stage 2 (green), stage 3 (blue), and REM sleep (magenta). Coma cluster is well separated from wakefulness and sleep clusters.

Figure 2: Summary scatter plots of all coma EEG recordings for patients with good outcome (A) and poor outcome (B). State space clusters are plotted on log/log axes for all subjects as shown in Figure 1. For better comparability all cluster centroids are transformed to the coordinate origin (0/0). Gray lines on both axes indicate probability density estimates of state space states for each subject. Patients with good outcome showed qualitatively higher spatial variability in both x- and y axes.

Figure 3: Mapping of average state space velocity in patients with good outcome (left panel) and poor outcome (right panel). State space velocity was significantly higher in temporal and frontal electrode locations (significant differences in Fp1 F8, T3, T4, T5, T1, T2, O1, black circles). Electrode positions according to the 10/20 system are shown as black dots (with linear interpolation on a Cartesian grid).

Figure 4: State space velocity as predicting factor. (A) Correlation of temporal state space velocity with clinical outcome (CPC scale). Higher velocity correlated linearly with better outcome ($R=0.37$, $p=0.003$). (B) Receiver operating characteristic (ROC) analysis for state space velocity as a potential biomarker for outcome prediction. Each point on the curve represents the sensitivity (true-positive rate) and false-positive rate (1 - specificity) associated with a particular value for state space velocity to predict poor outcome after cardiac arrest (Point A: limit = 0.7, high sensitivity/low specificity. Point B: limit = 0.5, low sensitivity/high specificity. The chosen limit values are shown in panel (A) as horizontal dotted blue lines.

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